CARBON ALKYLATIONS WITH CERTAIN TERTIARY AMINES AND QUATERNARY AMMONIUM SALTS

BY

ROBERT EDWARD CARNAHAN

B.S., University of Wisconsin, 1947
M.S., University of Illinois, 1948

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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Introduction

Examples of the alkylation of active methylene compounds by Mannich bases have been known for a number of years. In these reactions the Mannich base has been regarded as a source of α,β-unsaturated compound (usually ketone) to which the active methylene compound added in the Michael fashion. Quaternary ammonium salts of this type of amine as well as quaternary salts of amines which are not Mannich bases have been used similiary. One of these is 1-methylgramine, a compound which cannot react by an elimination-addition mechanism. This amine and its quaternary salt have been shown to react by an ionic substitution mechanism (1). Recently an alkylation of an ester containing an active methinyl group by benzyldimethylamine, an amine which cannot react by an elimination-addition mechanism, was observed (1). It seemed desirable to discover by what path this alkylation took place so that extensions of the reaction could be projected, and so that this alkylation could be correlated with the types already observed.

Recently Grignard reagents have been added to the list of anionic reagents that can be alkylated by gramine methiodide and 1-methylgraminemethiodide (1). These reactions led to the formation of 3-substituted indoles. The amplification of this reaction to provide a general method for the synthesis of substituted indoles as well as to apply it to other quaternary ammonium compounds would create a useful synthetic tool. Therefore, a study of the reaction was undertaken.

The vital step in a recent synthesis of tryptophan was the alkylation of indole by piperidinomethylformaminomalonic ester (2). Since this was the first report of such an alkylation, some exploratory reactions were carried out to determine the possibility of applying other tertiary amines and quaternary

ammonium salts to the alkylation of indole.

Discussion of Results

Benzyldimethylamine has been found to alkylate methyl cyanoacetate. The first step in the reaction mechanism is the quaternization of the amine by the ester. Alkylation then proceeds with the evolution of trimethylamine and carbon dioxide to yield hydrocinnamonitrile and dibenzylacetonitrile. The alkylations of methyl cyanoacetate by 1-methylgramine and of tricarbethoxymethane by benzyldimethylamine (1) were found to take place with the evolution of a tertiary amine. This was taken as evidence that quaternization is also the first step in the mechanism of these reactions. The ester, methyl benzylcyanoacetate, has been shown to be an intermediate in the formation of dibenzylacetonitrile, the dialkylation product, in the reaction between benzyldimethylamine and methyl cyanoacetate. A free radical mechanism for these alkylations has been shown to be untenable.

Considerable amounts of dibenzylmethylamine were produced in the alkylation of methyl cyanoacetate by benzyldimethylamine. This has been found to be the result of the disproportionation of benzyldimethylamine which takes place when it is heated in the presence of the benzyltrimethylammonium ion. Trimethylamine is also produced in the disproportionation. A cyclic process in which the benzyltrimethylammonium ion is regenerated has been proposed for the reaction. The dibenzyldimethylammonium ion is an intermediate in this process and has been shown to undergo the Stevens rearrangement (3) to α,β-diphenylethyldimethylamine in the presence of high concentrations of the cyanoacetate ion. Traces of acid will also cause the disproportionation of benzyldimethylamine, but to a lesser extent. Several other tertiary amines were tested, but benzyldimethylamine was the only one found to undergo the disproportionation in appreciable yield.

3-Benzylindole has been produced in 31.5% yield in the reaction between gramine methiodide and phenylmagnesium

bromide, while the alkylation of methylmagnesium iodide by gramine methiodide yielded 3-ethylindole in 15.1% yield. Benzylmagnesium chloride has been used in a similar reaction and found to yield 3-(β-phenylethyl)-indole, the structure of which was proven by oxidation to benzoic acid. Gramine has been found to be essentially unreactive toward the Grignard reagent. *o*-Dimethylaminomethylphenol, benzyltrimethylammonium chloride, benzylpyridinium chloride, and 2-dimethylaminomethylpyrrole methiodide have failed to alkylate Grignard reagents. Alkylation of phenyllithium and *p*-tolylmercuric chloride by 1-methylgramine methiodide failed.

Benzyltrimethylammonium chloride failed to alkylate indole in boiling xylene with sodium hydroxide as a catalyst. However, N-alkylation of indole took place when the potassium derivative was heated with benzyltrimethylammonium chloride.

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VITA

The author was born on January 5, 1925, in Kaukauna, Wisconsin. He attended the public schools of Madison, Wisconsin, and was graduated from Madison East High School in 1942. He entered the University of Wisconsin in September of that year and was in attendance there until he entered the United States Navy in July, 1944. He served in the American and Pacific Theaters, and received his discharge in May, 1946, at which time he reentered the University of Wisconsin and received the Bachelor of Science (Chemistry) degree in May, 1947. In September of that year he entered the Graduate College of the University of Illinois where he held a half-time teaching assistantship from September, 1947, to August, 1948, a University Fellowship from September, 1948, to June, 1949, and the Minnesota Mining and Manufacturing Company Fellowship during the academic year 1949-1950.

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